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"Dual-gene" malaria-resistance: Therapeutically-rational exchange (T-REX) of group-O sickle trait and group-O C-trait red blood cells can be evaluated in Benin and Nigeria

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Abstract

Background: Using indicators of disease severity, clinicians can predict which *Plasmodium falciparum* (*Pf*) malaria patients being treated with artesunate or quinine are likely to die despite these drugs. Effective "rescue adjuncts" are needed when drugs alone are inadequate. "Therapeutically-rational exchange" (T-REX) of special malaria-resistant red blood cells (RBCs) has been proposed to optimize adjunctive exchange transfusion.

Methods: Studies were reviewed that (1) quantified how group-O status and "sickle-trait" (HbAS) and "C-trait" (HbAC) hemoglobins affect *Pf* mortality, risk of thrombosis, or birth outcomes for women with pregnancy associated malaria (PAM), (2) reported prevalences of "dual-gene" malaria-resistant RBCs, or (3) reflected the level of exchange-transfusion and malaria-related expertise in Benin and Nigeria.

Results: Data show that the malaria- and thrombosis-resistance of RBCs depend on specific genes and the patient's clinical status and medical history. In malaria-endemic Benin and Nigeria, prevalences of "dual-gene" malaria-resistant group-O HbAS and group-O HbAC RBCs are substantial, and both malaria- and exchange-related expertise are outstanding.

Conclusions: T-REX of "dual-gene" malaria-resistant RBCs is feasible in Benin and Nigeria and warrants evaluation as a rescue adjunct for 3 subsets of *Pf* -malaria patients. For therapeutic use, group-O HbAS RBCs are likely to be more effective than non-O HbAS RBCs for *Pf* -infected patients who (1) have a history of thrombosis or (2) are taking birth-control hormones while group-O HbAC RBCs may substantially improve birth outcomes for women with PAM. Studies suggest it is prudent to assume – until proven otherwise – that T-REX of "dual-gene" malaria-resistant RBCs can improve ("personalize") rescue of these patient subsets.

Declaration of Competing Interest

Dr. Ryan Jajosky is the CEO and part-owner of Biconcavity Inc. Dr. Philip Jajosky is CMO and part-owner of Biconcavity Inc. Biconcavity Inc. is a biotechnology research and development company exploring drug-linked-erythrocytes. Biconcavity does not have any interest in malaria. Visit www.biconcavity.com for more information. Dr. Audrey Jajosky does not have any disclosures.

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1. Overview

As a treatment adjunct for patients with life-threatening *Plasmodium falciparum* (*Pf*) malaria, therapeutically-rational exchange (T-REX) refers to removing a patient's *Pf* -infected red blood cells (RBCs) and delivering (only) special malaria-resistant RBCs. We have previously suggested T-REX strategies be evaluated as "rescue adjuncts" when state-of-the-art drug therapies are inadequate [123]. T-REX of group-O RBCs and T-REX of "sickle-trait" hemoglobin-AS (HbAS) RBCs are 2 examples. Fortunately, in malaria-endemic Benin and Nigeria, 3 categories of malaria-resistant RBCs are prevalent: "sickle-trait" (HbAS), group-O, and "C-trait" (HbAC) RBCs [4 , 5].

The rationale for T-REX is simple: The same malaria-resistant RBCs that have promoted human survival may also promote patient survival when used therapeutically [6 , 7]. Recently, the therapeutic value of donated disease-resistant cells has been highlighted by the historic success of "the Berlin patient" [8]. So, it has been shown that patients do not have to be born with disease-resistant cells to benefit from them. Because malaria has driven human evolution for centuries, several different – and potent – malaria-resistant RBC variants are available [7]. "Malaria-resistance genes" are so prevalent in sub-Saharan Africa (SSA), many residents have co-inherited 2 RBC malaria-resistance genes. This means exchange transfusions of their donated "dual-gene" RBCs could be life-saving for especially vulnerable subsets *Pf* patients since the (different) anti-malaria benefits of group-O and HbAS and HbAC RBCs are independent – no reports of "negative epistasis" [4 , 5 , 9].

Regarding controversy about the therapeutic value of exchange, the confusion is understandable because only "standard issue exchange" has ever been evaluated in meta-analyses – and without any adjustment for mortality-impacting "confounders" [10 , 11]. That is, "RBC malaria-resistance variables" were not taken into account – unfortunate because ABO status and hemoglobin-type markedly impact *Pf* -malaria mortality [6 , 12]. The (numerous) case reports describing the successful recovery of near-death *Pf* -malaria patients following exchange may mean those (lucky) patients were treated (randomly and unknowingly) with malaria-resistant RBCs. The patients who died despite exchange may have been treated with RBCs that promoted *Pf* -disease progression. T-REX studies that separately evaluate the impact of specific malaria-resistant RBC variants can avoid such confounding in "the design phase" of clinical trials.

Because the different anti-malaria benefits of group O and HbAS and HbAC RBCs in Benin and Nigeria are independent, we feel "dual-gene" T-REX may markedly optimize anti-malaria exchange. Of note, data suggest some "dual-gene" exchange strategies would be prudent for 3 *Pf* -patient subsets: (1) women with pregnancy associated malaria (PAM), (2) women who are using hormonal contraception, and (3) patients with a history of thrombosis [5 , 131415]. Surprisingly, for PAM, researchers found that "hemoglobin C-trait" (HbAC) RBCs are associated with better birth outcomes than sickle-trait (HbAS) RBCs – even though HbAS RBCs might be the most potently malaria-resistant for all other patients [5]. Other studies suggest T-REX of "dual-gene" malaria-resistant group-O HbAS RBCs would be more prudent than delivering non-O HbAS RBCs to *Pf* -malaria patients who are taking

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birth-control hormones or have a history of deep-vein thrombosis or other thrombotic events [14 , 15].

2. History of transfusion in sub-Saharan Africa (SSA)

In SSA, adjunctive blood transfusions have been used to rescue malaria patients since 1892 [16]. Regarding technical expertise, the exchange-transfusion procedure has been used in Nigeria at least since 1963 [17]. In Benin, exchange has been used to treat challenging patients such as pregnant women with sickle cell disease [18].

In 21 st SSA, *Pf* -malaria patients are a major category of blood-transfusion recipients [19]. Unfortunately, when anemic *Pf* -infected patients are transfused with “standard issue” units, they may randomly receive malaria-promoting RBCs while uninfected patients may be receiving malaria-resistant RBCs. Also unfortunate, demand for blood often exceeds supply [20]. Fortunately, in 2017, Bates et al. proposed innovative ways to not only recruit and retain blood donors but to excite and motivate clinicians, researchers, students, and blood-bank technicians to advance transfusion medicine [21]. Their donation-promoting and research-based suggestions are incentive-based, exciting, and creative [21]. Here we call their goals “PAIRD” (Promote, Advance, Incentivize, and Reward Donation).

3. Clinicians in SSA are ideally positioned to evaluate T-REX of malaria-resistant RBCs

Nigeria is, arguably, the world leader in clinical research related to *Pf* malaria, RBC genetic variants, and exchange transfusion [4 , 15 , 29–35 , 17 , 22–28]. To our knowledge, the first-and-only study of variant-specific RBC exchange transfusions was conducted by Nigerian pediatricians in 1981 [29]. The RBC variants they exchanged to treat hospitalized neonates were chosen because they are prevalent in malaria-endemic Nigeria – not surprisingly, these variants were malaria-resistant variants [29]. Malaria-resistant RBCs are so prevalent in SSA that even “dual-gene” prevalences are substantial: Among 533 inpatients in Benin and 300 in Nigeria, prevalences of group-O HbAS RBCs were 8.4 % and 6.0 %, respectively, while group-O HbAC RBCs prevalences were 5.4 % and 1.3 % [4 , 5]. This means “dual-gene” malaria-resistant RBCs should be available for therapeutic use in Benin and Nigeria even without active recruitment of donors.

So, with the support of hospital managers, transfusion-medicine physicians, and blood-bank personnel, clinicians in Benin and Nigeria are well positioned to evaluate how “dual-gene” T-REX strategies might personalize the rescue of special subsets of *Pf* -malaria patients. For clinicians who worry about using HbAS RBCs therapeutically, Niazi and Fleming noted HbAS carriers in Nigeria “appear to be acceptable as blood donors” – and others agree [28–30].

Because of their extensive experience with *Pf* malaria and RBC variants and exchange transfusion, clinicians and researchers in Benin and Nigeria are ideally situated to evaluate T-REX, including “dual-gene” T-REX [5 , 18 , 29]. Regarding potential global interest, in a commentary about the protection provided by HbAS and HbAC RBC variants, an

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apparently frustrated Williams noted that, despite well-documented genetic associations with many diseases, “disappointingly few have delivered on the promise to revolutionize treatment” [36]. Interestingly, while Cohen et al. hope malaria-combating microRNAs can eventually be used to treat *Pf*-malaria, clinicians in SSA can immediately deliver microRNAs via T-REX of HbAS RBCs given that HbAS RBCs contain *Pf*-combating microRNAs [2 , 37 , 38]. Apparently disturbed by the unrelenting death caused by cerebral malaria, in 2019 Luzolo and Ngoyi suggested “A combination of two or more adjunctive therapies, appropriately selected, could perhaps prove to be effective; however extensive research and clinical trials will be necessary to determine such” [39]. Regarding cost, after describing how exchange transfusions had successfully rescued his *Pf*-malaria patients, Boctor suggested exchange might be cost-effective: “the expense is much lower than that of keeping patients in ICUs” [40].

4. T-REX of “dual-gene” malaria-resistant RBCs for 3 especially vulnerable subsets of *pf* patients

In Nigeria, Ahmed et al. found that although sickle trait (HbAS) – overall – is only a weak risk factor for deep-vein thrombosis (DVT), there was a higher risk of DVT among sickle-trait patients whose HbAS RBCs were of a non-O ABO blood group [15]. Although their study subjects were not infected with *Pf*-malaria, it seems most prudent to assume – until proven otherwise – that non-O HbAS RBCs are also “prothrombotic” for *Pf*- malaria patients who have a history of thrombosis [15]. Ahmed et al. concluded co-inheritance of the non-O blood group and sickle trait (HbAS) is “an important mixed risk factor for DVT” [15]. Of course, non-O HbAS RBCs may not actually be “prothrombotic” for *Pf*- malaria patients given that HbAS RBCs are – overall – known to substantially reduce the risk of cerebral microvascular thrombosis (cerebral malaria) [414243]. Despite this apparent paradox, it seems most prudent that when clinicians want to use HbAS RBCs therapeutically, they only use group-O HbAS RBCs when treating *Pf*-malaria patients who have a history of thrombosis – in “an abundance of caution.”

Also thrombosis-related, Austin et al. concluded that women with HbAS RBCs who use hormonal contraception are at increased risk for venous thrombotic events [14]. Although the women they studied were not infected with *Pf*, it again seems prudent that when using HbAS RBCs therapeutically, only group-O HbAS RBCs be used when treating *Pf*- infected women who are taking birth-control hormones.

Surprisingly, Tetard et al. found that sickle-trait (HbAS) RBCs do not improve birth outcomes for women with PAM [5]. Fortunately – in contrast to HbAS RBCs – malaria-resistant “C-trait” (HbAC) RBCs are linked to better birth outcomes [5]. So, for PAM, it seems prudent that clinicians only transfuse malaria-resistant HbAC RBCs (and never HbAS RBCs). Loscertales and Brabin found that malaria-resistant group-O RBCs can also improve birth outcomes for women with PAM [13]. Fortunately, T-REX of “dual-gene” malaria-resistant group-O HbAC RBCs might be substantially more effective than T-REX of non-O HbAC RBCs because the individual (and independent) group-O and HbAC anti-*Pf* benefits should be additive. That is, to our knowledge, researchers have never found

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"negative epistasis" (cancellation of anti-malaria benefits) between group-O RBCs and malaria-resistant hemoglobins when statistical modeling has included these RBC "malaria-resistance variables" [9]. Addition of these therapeutic benefits is fortunate because the individual anti-malaria protections provided by group-O RBCs and HbAC RBCs are considered weaker than the very potent malaria-resistance of sickle-trait HbAS RBCs [42].

In general, when requesting transfusions for patients with life-threatening *Pf* malaria who do not have PAM, clinicians should know HbAS RBCs are thought to be the most potently malaria-resistant RBCs [42]. After Taylor et al. reviewed malaria studies, they noted "data from both case-control and prospective cohort studies indicate that HbAS is consistently associated with large reductions in the risk of severe malaria syndromes" [42].

5. Evaluation of T-REX in Benin and Nigeria: an "Ideal PAIRD project"?

Noting that "lack of access to adequate blood supplies" is an "urgent problem" in SSA, Bates et al. proposed incentive- and reward-based agendas in their article "Transfusion research priorities for blood services in sub-Saharan Africa" [21]. Among their PAIRD-oriented suggestions, they recommend working to (1) create donation- and research-conducive environments, (2) recruit, register, reward, and motivate new donors, (3) convince blood-services departments to promote research, (4) collaborate with local universities, (5) encourage, publicize, and recognize clinician, scientist, and graduate-student research, (6) promote international partnerships, and, of course, (7) support and advance anti-malaria agendas [21]. Although Bates et al. stressed policy improvements, we feel evaluating new RBC therapies – like T-REX – would also substantially advance transfusion medicine by motivating not only clinicians and blood donors locally, but also researchers inside and outside Africa. How? Given their expertise with both malaria and exchange, with adequate support, clinicians in SSA can easily evaluate T-REX [18 , 24 , 25 , 29]. If T-REX proves to be a life-saving adjunct, that success could highlight the importance of transfusion medicine. Because success with T-REX in SSA would show how human evolutionary genetics can be translated into practical cell therapies, T-REX could attract the attention of researchers in nations where malaria and other tropical diseases are not endemic and where RBC variants are not prevalent. Because some T-REX options – like some "dual-gene" T-REX strategies – would probably require recruitment and registration of "contactable donors," evaluation of T-REX would surely highlight the value of pursuing PAIRD-oriented initiatives. [21]. That is, T-REX and PAIRD-oriented recommendations seem, fortunately, especially complementary [21].

6. Conclusions

For *Pf* -malaria patients who do not adequately respond to artesunate or quinine treatments, their likelihood of dying can be predicted using "indicators of disease severity" – and can exceed 50 % [44]. Because data suggest exchange transfusion can be substantially (1) optimized and (2) personalized by thoughtfully delivering special malaria-resistant RBCs, we feel T-REX should be evaluated – now. Fortunately, both group-O and HbAS RBCs markedly promote survival, and, for PAM, both group-O and HbAC RBCs have been linked to better birth outcomes [5 , 6 , 12 , 13 , 45]. So, it is plausible T-REX of malaria-resistant

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RBC variants may be markedly more therapeutic than conventional exchange since current use of a blood bank's nondescript "standard issue" units means, unfortunately, malaria-promoting RBCs are, inevitably, being delivered – blindly and randomly. Data also suggest T-REX of "dual-gene" malaria-resistant group-O HbAS RBCs and/or group-O HbAC RBCs may effectively "personalize" T-REX for 3 vulnerable subsets *Pf*-infected patients. When using HbAS RBCs therapeutically – perhaps the most potent malaria-resistant RBC variant – only T-REX of "dual-gene" group-O HbAS RBCs should be used for *Pf*-malaria patients who (1) are taking birth-control hormones or (2) have a history of thrombosis because non-O HbAS RBCs might be "pro-thrombotic" for these 2 subsets [14 , 15 , 45]. For challenging PAM, T-REX of "dual-gene" group-O HbAC RBCs should be used because both group-O and HbAC RBCs have been linked to better birth outcomes [5 , 13].

The potential benefits of evaluating T-REX in SSA are exciting: Adjunctive T-REX may (1) reduce *Pf* morbidity and mortality, (2) advance transfusion medicine, (3) generate interest in translating evolutionary genetics into practical therapies, and (4) attract the international sponsorship of research only possible in SSA – goals explicitly or implicitly advocated by prominent researchers [456 , 18 , 21 , 36 , 46]. Evaluating T-REX in SSA seems (1) warranted (*Pf*-infected patients are dying despite drug treatment) and (2) feasible (a variant-specific RBC exchange study was conducted in Nigeria in 1981) [29 , 44]. Finally, Maitland is correct: Regarding management of severe *Pf* malaria in SSA, she concluded "high-quality trials can be undertaken" – but, lamented, "the slow progress in this field is astonishing" [46].

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